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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,413	12/17/1999	ALBERTO A. GABIZON	5325-0161.30	2363

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/467,413	Applicant(s) Gabizon
	Examiner Gollamudi Kishore, Ph.D	Art Unit 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 25, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12, 22, and 23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12, 22, and 23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time and amendment dated 8-25-03 are acknowledged.

Claims included in the prosecution are 1-12 and 22-23.

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Mislick et al (Bioconjugate Chemistry, 1995) of record.

Mislick teaches the delivery of folate-polylysine-DNA complexes to carcinoma cell cultures (note the entire publication).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that there is no teaching in Mislick of administration of an agent to multi-drug resistant cell and that the examiner is making a leap. This argument is not found to be persuasive since Mislick uses KB cells derived from a human nasopharyngeal carcinoma (high folate receptors). A careful review of the specification indicates that applicant uses the same cell line (page 30, lines 18-21). Furthermore, it

would appear from Mislick that the drug has accumulated in the cell and not prevented from accumulation due to the action of the efflux pump (p-glycoprotein, see instant specification on page 10, line 1 et seq.). The burden therefore, is shifted to applicant to show evidence that the cells used by Mislick are not multi-drug resistant.

3. Claims 1-2 , 4-12 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al, (BBA, 1995) of record.

Lee discloses folate-PEG-DSPE liposomes which contain doxorubicin and administration of this composition to several carcinoma cell lines; the molecular weight of PEG is 3350 (note the abstract and Materials and Method section).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are similar to those for Mislick's reference and therefore, the same response is deemed applicable. Lee uses KB cells just as in Mislick above.

4. Claims 1-2 and 4-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Goren (1997) or Horowitz (1997) of record.

Both Goren and Horowitz teach the administration of folate-DSPE-liposomes containing doxorubicin to carcinoma cell lines (note the entire publications).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that there is no teaching or suggestion in

Goren of a method of administering an agent to a multi-drug resistant cell and that the examiner aussumes that the tumer cells of Goren are associated with a multi-drug neoplastic condition. This argument is not persuasive since Goren uses M109 drug resistant cell line just as in instant application. It is also interesting to note that applicant's experiments concern with free doxorubicin just as in Goren (see page 8 of instant application). Furthermore, as stated above, it would appear from Goren that the drug has accumulated in the cell and not prevented from accumulation due to the action of the efflux pump (p-glycoprotein, see instant specification on page 10, line 1 et seq.). The burden therefore, is shifted to applicant to show evidence that the cells used by Goren are not multi-drug resistant.

Applicant's arguments with regard to Horowitz are similar to those put forward for Goren; these arguments are not persuasive since just as Goren, Horowitz uses M109 cells just as in instant application.

Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2 , 4-12 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (BBA) or Goren (1997) or Horowitz (1997) of record cited above.

Lee, Goren and Horowitz do not specifically teach in vivo administration of the composition for the treatment of neoplastic diseases. However, it would have been obvious to one of ordinary skill in the art to administer the composition in vivo, with a reasonable expectation of success, based on the in vitro studies of the prior art. Although Lee, Goren, and Horowitz do not teach other therapeutic agents, it is deemed obvious to one of ordinary skill in the art to use any therapeutic drug with the expectation of obtaining similar results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the lack of teachings of Multi-drug resistance of the cancers and these have been addressed above. Even asssuming that the cells are not MDR cells since these references are clearly suggestive of folate mediated targeting of the same claimed drugs and therefore, one of ordinary skill in the art would be motivated to extrapolate the studies to MDR cells with a reasonable expectation of success.

7. Claims 1-3, 6-12 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mislick cited above, in view of Lee et al (BBA) or Goren (1997) or Horowitz (1997) of record cited above individually or in combination.

Mislick teaches nucleic acid as the active agent in the folate conjugates and not instant therapeutic agents. However, it would have been obvious to one of ordinary skill in the art to use any therapeutic agent since that depends on the nature of the disease.

One of ordinary skill in the art would be motivated to use instant chemotherapeutic drugs since the references of Lee, Goren and Horowitz show the routine practice in the art of using these drugs.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that none of the references teach or suggest that the administration of a folate targeted drug conjugate would be effective to achieve accumulation of the drug in MDR cells. This argument is not found to be persuasive since as pointed out above, a careful review of the specification indicates that applicant uses the same cell line (page 30, lines 18-21). Furthermore, it would appear from Mislick that the drug has accumulated in the cell and not prevented from accumulation due to the action of the efflux pump (p-glycoprotein, see instant specification on page 10, line 1 et seq.). Even asssuming that the cells are not MDR cells since these references are clearly suggestive of folate mediated targeting of the anti-neoplastic drugs and therefore, one of ordinary skill in the art would be motivated to extrapolate the studies to in vivo situations where the cancer involves MDR cells, with a reasonable expectation of success.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ***G.S. Kishore*** whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**thurman.page@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

November 14, 2003